Accessing Novel Process Windows in a High-Temperature / Pressure Capillary Flow Reactor

C. Oliver Kappe
Christian Doppler Laboratory for Microwave Chemistry (CDLMC)
and Institute of Chemistry, University of Graz
Heinrichstrasse 28, A-8010 Graz, Austria
oliver.kappe@uni-graz.at
www.maos.net

Christian Doppler Laboratory for Microwave Chemistry (CDLMC)
University of Graz, Austria – www.maos.net

Advantages of Flow Chemistry - Microreactors

- Very efficient mixing of the reactants (micromixing)
- Rapid heat transfer and temperature control of the reaction system
- High temperature/high pressure capability
- Automated reaction optimization – on the fly changes
- Multi step reactions in a continuous sequence
- Immobilized catalysts/reagents
- Easy scale-up of a proven reaction by:
  - increase of time
  - reactor volume change
  - parallel processing (numbering up)
- Automated purification possible by:
  - solid phase scavenging
  - chromatographic separation
  - liquid/liquid extraction
- Integrated screening (lab-on-a-chip)

Microreactor Chip for Flow Processing

Advantages of High Temperature Flow Chemistry

- Very efficient mixing of the reactants (micromixing)
- Rapid heat transfer and temperature control of the reaction system
- High temperature/high pressure capability
- Automated reaction optimization – on the fly changes
- Multi step reactions in a continuous sequence
- Immobilized catalysts/reagents
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  - increase of time
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- Automated purification possible by:
  - solid phase scavenging
  - chromatographic separation
  - liquid/liquid extraction
- Integrated screening (lab-on-a-chip)

Tube/Capillary Reactor For Flow Processing ("Mesofluidic")

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Process Intensification Technologies (Novel Process Windows)

- Routes at elevated temperature and/or pressure
- Routes mixing reagents "all at once"
- Routes at increased concentration or solvent free
- Direct routes from hazardous elements
- Routes using unstable intermediates
- Routes in the explosive or thermal runaway regime
- Process simplification (routes avoiding catalysts or complex separations)

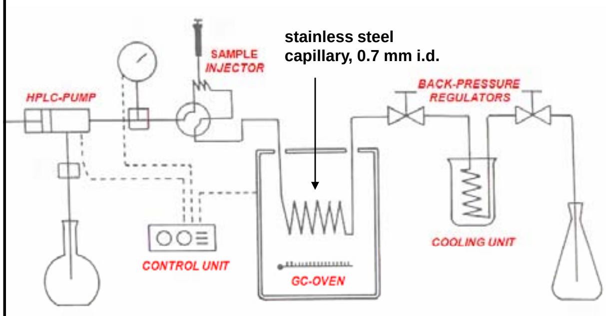
Jähnisch, K.; Hessel, V. et al. *Angew. Chem. Int. Ed.* **2004**, *43*, 406-446
Hessel, V.; Löb, P.; Löwe, H. *Curr. Org. Chem.* **2005**, *9*, 765-787
Hessel, V.; Kralisch, D.; Krtschil, U. *Energy Environ. Sci.* **2008**, *1*, 467-478

Van Gerven, T.; Stankiewicz, A. *Ind. Eng. Chem. Res.* **2009**, *48*, 2465

Can Microwave (Batch) Chemistry be Translated to Flow Conditions?
Short Reaction Times = Short Residence Times

Background: High Temperature/Pressure Flow Chemistry in Steel Capillary Reactors

Reactor Combining HPLC and GC Parts



Chemistries

- Redox chemistry
- Radical reactions
- Ester pyrolysis
- Degradation of cellulose and chitin
- Supercritical conditions

Selected References (J. O. Metzger, 1978-1991)

Köll, K.; Metzger, J. *Angew. Chem.* **1978**, *90*, 802; Metzger, J.; Köll, K. *Angew. Chem.* **1979**, *91*, 74; Malwitz, D.; Metzger, J.O. *Angew. Chem.* **1986**, *98*, 747; Metzger, J. *Angew. Chem.* **1983,** *95*, 914; Klenke, K.; Metzger, J. O.; Lübben, S. *Angew. Chem.* **1988**, *100*, 1195; Giese, B.; Farshchi, H.; Hartmanns, J.; Metzger, J. O. *Angew. Chem.* **1991**, *103*, 619.

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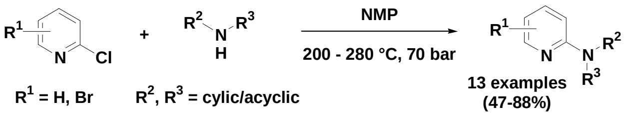
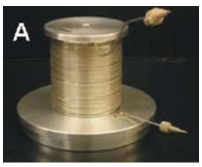
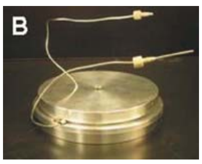
Background: High Temperature Flow Chemistry in Steel Capillary Reactors

S_NAr Substitutions with Secondary Amines

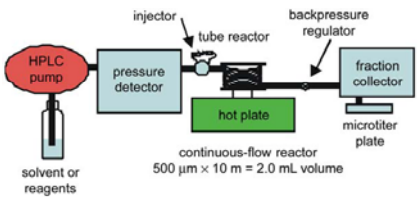




Aluminium Spool
44 turns, 10 m
0.5 mm i.d. stainless steel



Flat Aluminium Reactor
10 m
0.5 mm i.d. stainless steel



Hamper, B.; Tesfu, E. (Pfizer, USA) *Synlett* **2007**, 2257

Commercially Available "Mesofluidic" Reactors for (High Temperature/Pressure) Organic Synthesis

UNIQSIS
FlowSyn
www.uniqsis.com

syrris
Africa
www.syrris.com

THALESNano
X-Cube Flash
www.thalesnano.com

vapourtec
R-Series Flow System
www.vapourtec.co.uk

AMTechnology
Coflore ACR
www.amtechuk.com

Advion
NanoTek
www.advion.com

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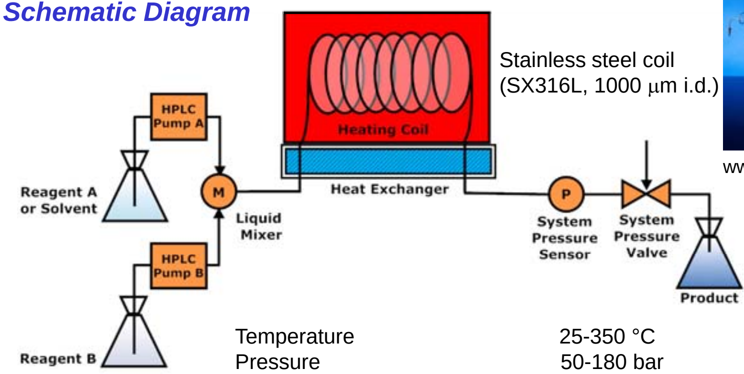
High-Temperature/Pressure Flow Reactor (X-Cube Flash)

www.thalesnano.com

Schematic Diagram



Temperature	25-350 °C
Pressure	50-180 bar
Flow rates	0.5-10 mL/min
Changeable size of reaction zone	4,8,16 mL

Razzaq, T.; Glasnov, T, N.; Kappe, C. O. *Eur. J. Org. Chem.* **2009**, 1321; *Chem. Eng. Technol.* **2009**, 32, 1702

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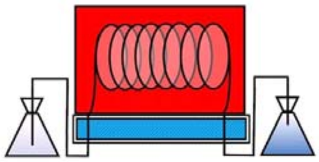
From Microwave Batch to Flow

Single-Mode Microwave | **Multimode Microwave** | **X-Cube Flash**

Optimization → **Batch Scale-Up** → **Continuous Flow Processing**

< 20 mL

~ 1 L



4, 8, 16 mL coils

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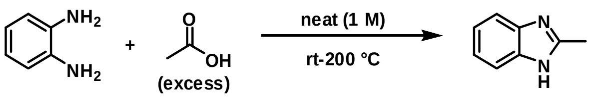
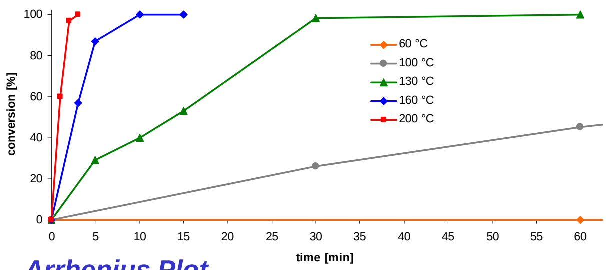
Case Study 1: 2-Methylbenzimidazole Formation

Kinetic Study

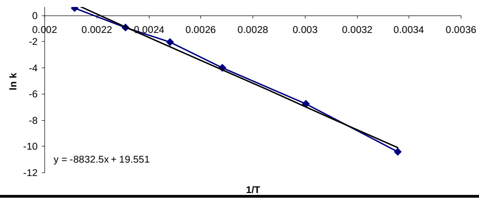




T [°C]	>99 % conv. after
25	9 weeks
60	5 days
100	5 h
130	30 min
160	10 min
200	3 min
270	"1 s"

Arrhenius Plot

- Activation energy:
  E_a = 73.43 kJ/mol
- Pre-Exponential factor:
  A = 3.1 x 10^8



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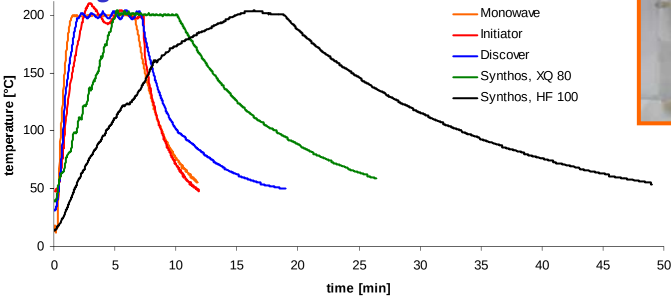
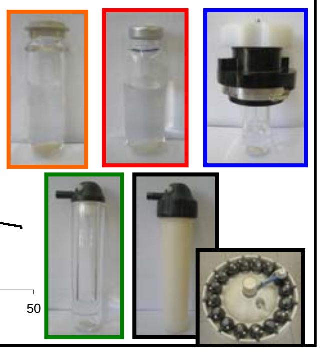
Batch Microwave Scale-Up: 2-Methylbenzimidazole (200 °C, 5 min, 5 M)

MW Instrument	Reaction volume (mL)	Yield in g (%)	Ramp/hold/cooling time (min)	Overall processing time (min)
Monowave 300	20	9.44 (95)	1/5/6	12
Initiator EXP 2.5	20	9.35 (94)	2/5/5	12
Discover LabMate	20	9.13 (92)	2/5/6	13
Synthos 3000 (XQ 80)	4 × 10 = 40	18.68 (94)	5/5/17	27
Synthos 3000 (HF 100)	16 × 60 = 960	465.7 (98)	15/5/30	50

Heating Profiles





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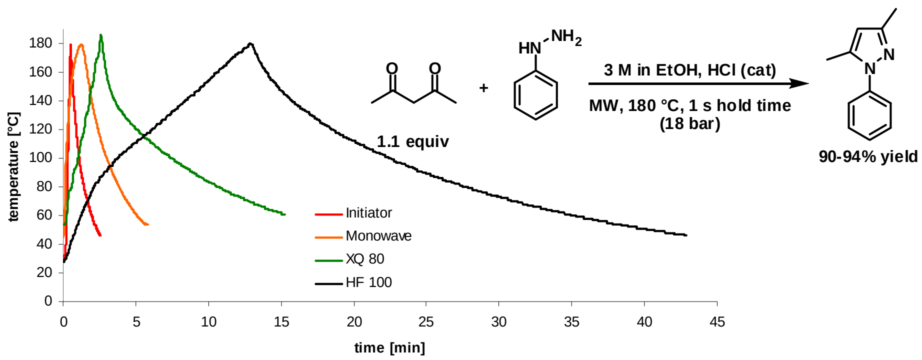
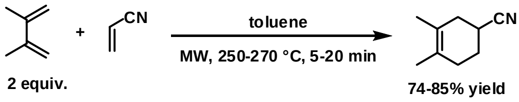
Case Study 2: Pyrazole Synthesis



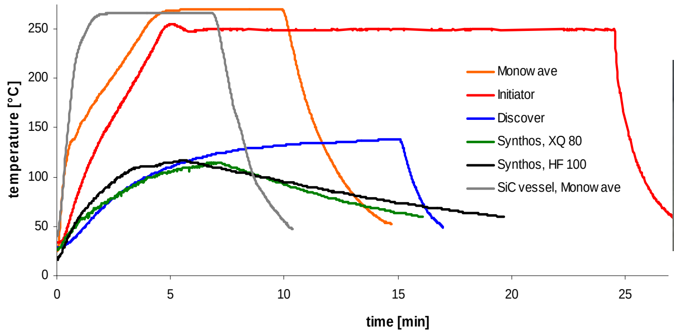
MW Instrument	Reaction volume (mL)	Yield in g (%)	Ramp/cooling time (min)	Overall processing time (min)
Monowave 300	20	9.40 (91)	1.5/4.5	6
Initiator EXP 2.5	20	9.29 (90)	<1/3.2	4
Synthos 3000 (XQ 80)	4 × 10 = 40	19.34 (94)	2.5/12.5	15
Synthos 3000 (HF 100)	16 × 60 = 960	468 (95)	13/30	43

Case Study 3: Diels-Alder Cycloaddition



- weakly MW absorbing mixture
- high temperatures can not be reached in multimode reactors
- high temperatures and rapid heating with SiC vials

Heating Profiles

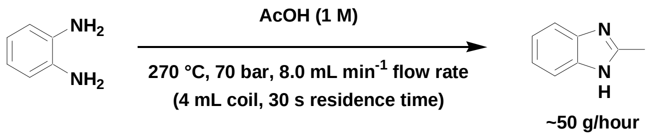


SiC Vials

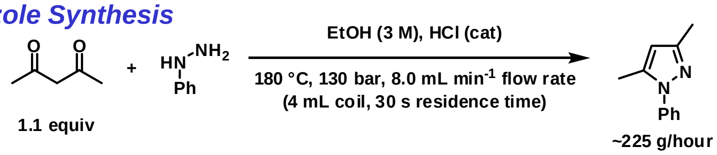
cf. *Angew. Chem. Int. Ed.* **2009**, *48*, 8321

Converting Batch Microwave to Continuous Flow Processing (X-Cube Flash)

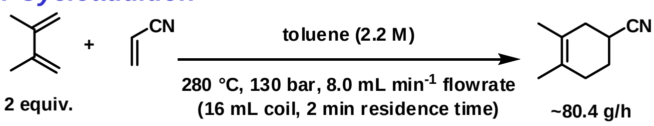
Benzimidazole Synthesis



Pyrazole Synthesis



Diels-Alder Cycloaddition



Damm, M.; Glasnov, T, N.; Kappe, C. O. *Org. Process Res. Develop.* **2010**, *14*, in press

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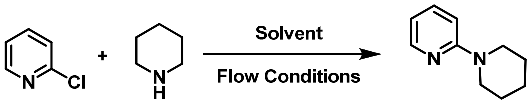
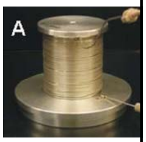
Chemistry Examples: High-T/p Flow Chemistry (1)

Nucleophilic Aromatic Substitution – Steel Capillary Reactor

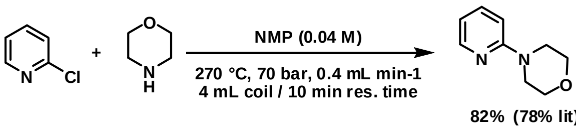




Piperidine, equiv.	Flow Rate, mL/min	Solvent	Temp., °C	Yield, %
1	0.5	DMF	240	47
2	0.5	DMF	240	52
2	0.1	DMF	240	63
2.2	0.1	DMA	260	76
2.2	0.1	NMP	260	100

cf. Hamper, B. C.; Tesfu, E. *Synlett* **2007**, 2257

Nucleophilic Aromatic Substitution – X-Cube FLASH



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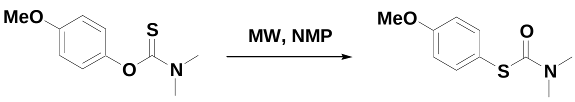
Chemistry Examples: High-T/p Flow Chemistry (2)

Newman-Kwart Rearrangement: Microwave Conditions



Moseley, J. D. et al. *Tetrahedron* **2006**, *62,* 4685
Moseley, J. D.; Lenden, P. *Tetrahedron* **2007**, *63,* 4120

280 °C, 20min: 27% (HPLC)
330-340 °C, 40 min: 99% (HPLC)

Continuous Flow Results (4 mL Coil)

NMP: 280 °C, 60 bar, 1 mL min^{-1} >99% (HPLC)
Isolation difficult (aqueous)

scDME: 300 °C, 80 bar, 1 mL min^{-1} >99% (HPLC)
(bp. 85 °C, critical point: 263 °C/38 bar)
Isolation by simple evaporation >99% yield

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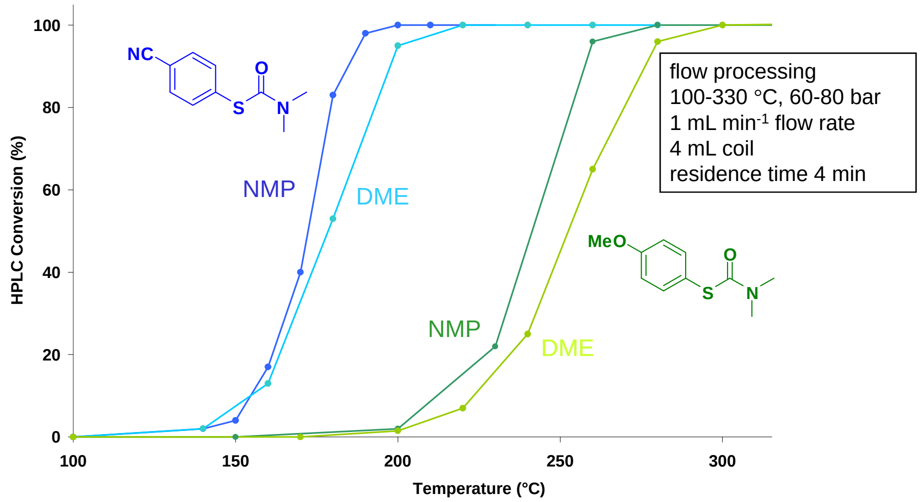
Continuous Flow Newman-Kwart Rearrangement

Kinetic Analysis (HPLC)



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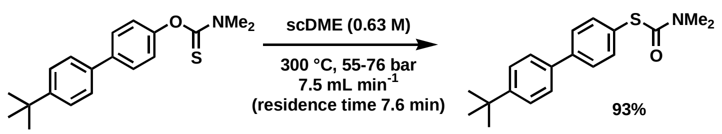
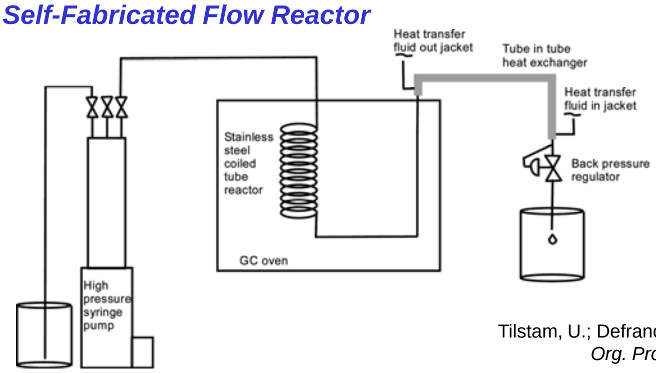
Continuous Flow Newman-Kwart Rearrangement (Eli Lilly, 2009)



Self-Fabricated Flow Reactor



Maximum Operating Conditions:
T : ~320 °C
p : ~137 bar

Tilstam, U.; Defrance, T.; Giard, T; Johnson, M. D. *Org. Process. Res. Dev.* **2009**, *13,* 321

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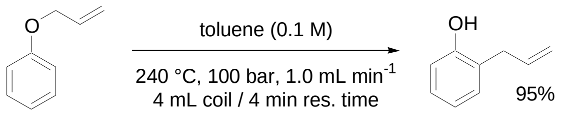
Chemistry Examples: High-T/p Flow Chemistry (3)

Claisen Rearrangement



cf. MW conditions (toluene, 250 °C, SiC): Kremsner, J. M.; Kappe, C. O. *J. Org. Chem*. **2006**, *71*, 4651
Razzaq, T.; Kremsner, J. M.; Kappe, C. O. *J. Org. Chem.* **2008,** *73,* 6321

Optimization in Flow

Solvents:	NMP, DMF, Toluene, *sc*EtOH, *sc*DME
Temperature Range:	140 – 325 °C
Flow Rates:	0.8 – 2 mL/min
Pressure:	60 – 125 bar

Best Conditions (Full Conversion, Cleanest Reaction Profile):

toluene (0.1 M), 240 °C, 100 bar, 1.0 mL min^{-1}

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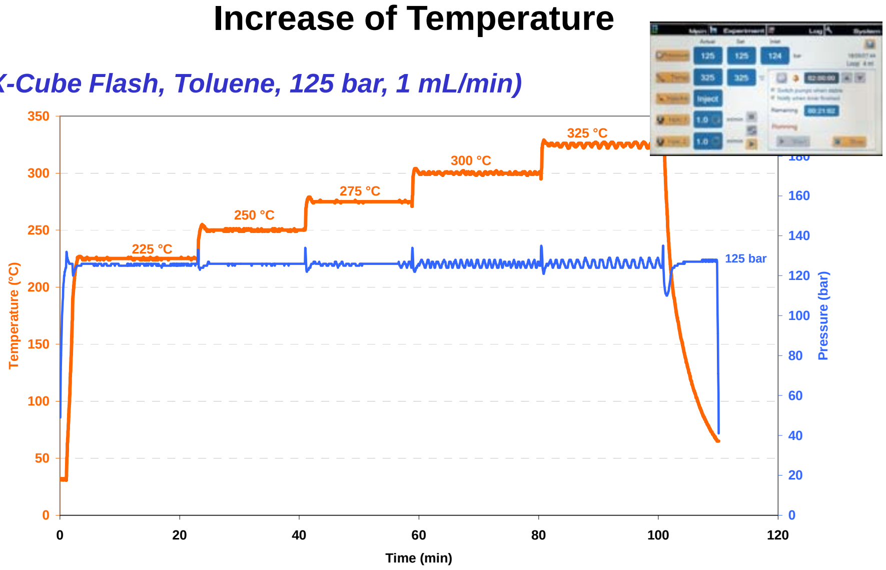
Claisen Rearrangement – Stepwise "On-the-Fly" Increase of Temperature

(X-Cube Flash, Toluene, 125 bar, 1 mL/min)



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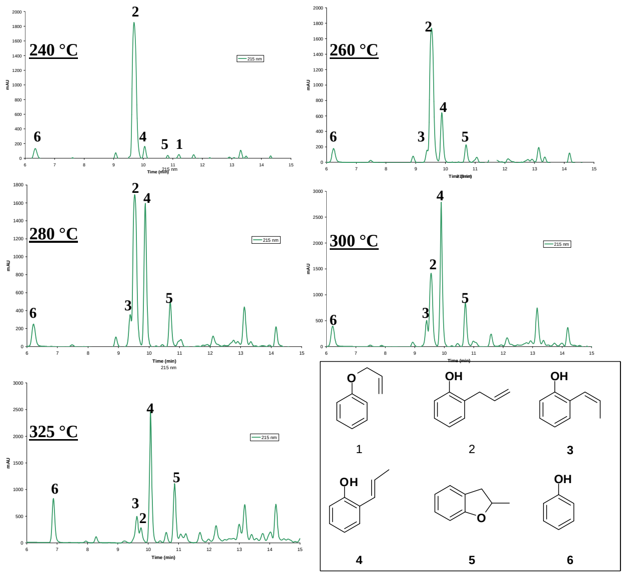
High-T/p Claisen Rearrangements in Toluene at Different T

HPLC Monitoring (GC-MS)

Conditions:
240-325 °C
100-125 bar
1ml/min flow
4 mL coil
4 min res. time



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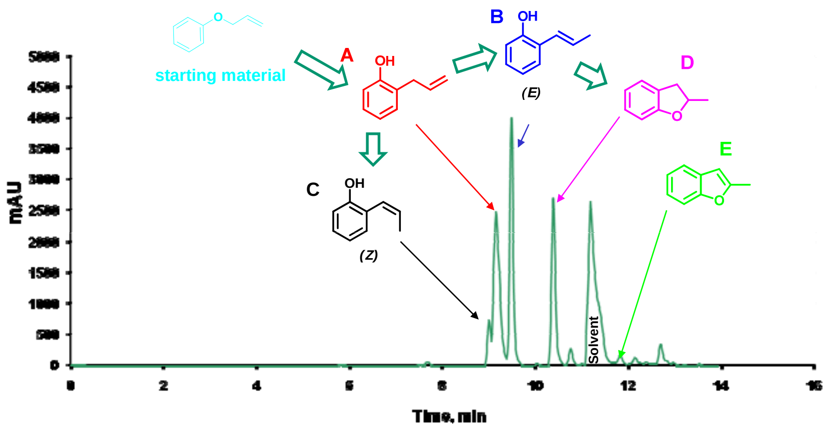
Claisen Rearrangement – High Temperature Reaction Pathways (Toluene, 315 °C)

HPLC Monitoring (GC-MS)



Razzaq, T.; Glasnov, T, N.; Kappe, C. O. *Chem. Eng. Technol.* **2009**, 32, 1702

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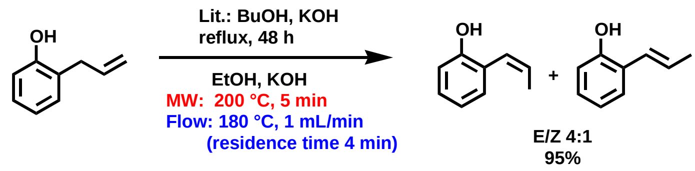
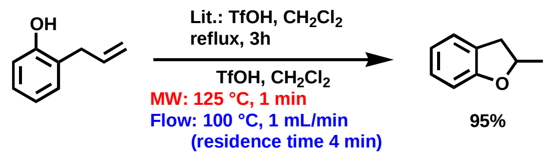
Chemistry Examples: High-T/p Flow Chemistry (4)

Base-Catalyzed Rearrangement of 2-Allylphenol



cf. Davies, N. R.; DiMichiel, A. D. *Aust. J. Chem*. **1973**, 26, 1529

Acid-Catalyzed Cyclization of 2-Allylphenol



cf. L. Coulombel, E. Dunach, *Green Chem*. **2004**, 6, 499

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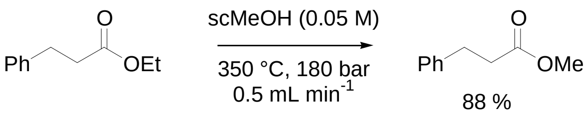
Chemistry Examples: High-T/p Flow Chemistry (5)
Reactions in Supercritical Alcohols

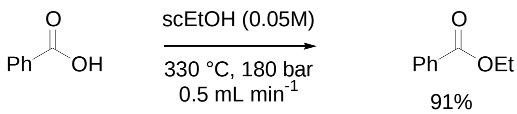
Transesterification



MeOH
T_c = 239 °C, P_c = 81 bar

cf. Socher, G. et al. *Fresensius J. Anal. Chem.* **2001**, *371*, 369

Esterification



EtOH
T_c = 268 °C, P_c = 61 bar

Razzaq, T.; Glasnov, T, N.; Kappe, C. O. *Eur. J. Org. Chem.* **2009**, 1321

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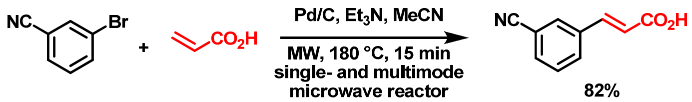
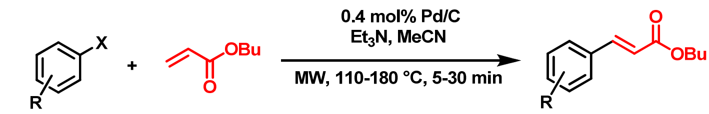
Chemistry Examples: Medium T/p Flow Chemistry Heck C-C Coupling

Literature Background



Stadler, A. et al. *Org. Process Res. Dev.* **2003**, *7*, 707
Degussa Pd/C: Köhler, K. et al. *Chem. Eur. J.* **2002**, *8*, 622

Example for Batch and Flow Chemistry



X = I, R = 4-CN
X = Br, 3-CN

cf. Nikbin, N.; Ladlow, M.; Ley, S. *Org. Process Res. Dev.* **2007**, *11*, 458 (monolithic nanoparticles)
cf. K. Mennecke, W. Solodenko, A. Kirschning, *Synthesis* **2008**, 1589 (immobilized palladacycles)

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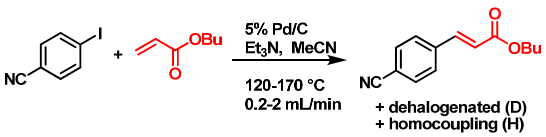
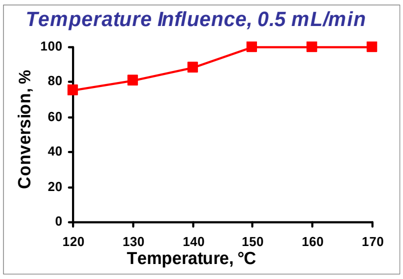
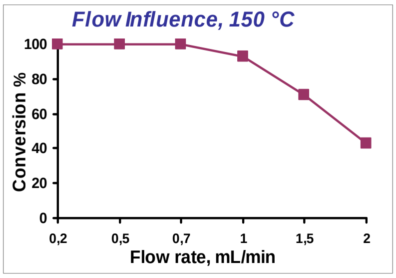
Heck Chemistry under Flow Conditions (Immobilized Catalyst: Pd/C)



X-Cube
(200 °C, 150 bar)





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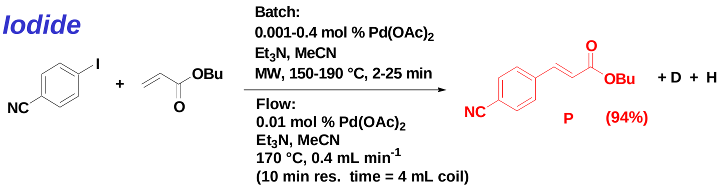
Heck Chemistry (MW / Flow) – Homogeneous Catalysis with $Pd(OAc)_2$

Aryl Iodide



Entry	Conditions	$Pd(OAc)_2$ [mol%]	Temp [°C] / Time [min]	Conversion [%, GC-FID]	Selectivity P/D/H [%, GC-FID]
1	Batch/MW	0.4	150 / 2	>99	89 / 5 / 6
2	Batch/MW	0.1	150 / 2	>99	93 / 2 / 5
3	Batch/MW	0.05	150 / 5	>99	98 / 1 / 1
4	Batch/MW	0.01	150 /25	>99	99 / <1 / 0
5	Batch/MW	0.01	170 / 10	>99	99 / <1 / 0
6	Batch/MW	0.001/ 10 mol% TBAB	190 / 15	>99	99 / <1 / 0
7	Batch/OB	0.01	150 / 25	>99	99 / <1 / 0

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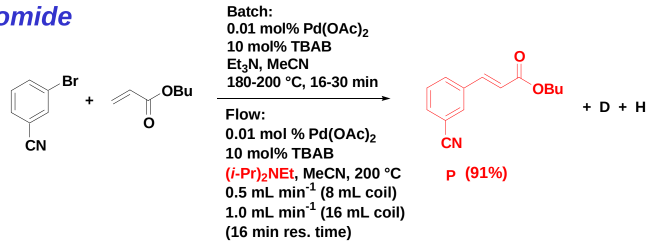
Heck Chemistry (MW / Flow) – Homogeneous Catalysis with $Pd(OAc)_2$

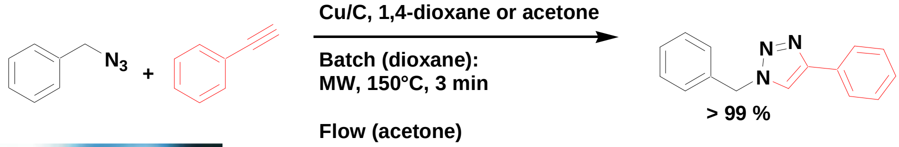
Aryl Bromide



Entry	Conditions	$Pd(OAc)_2$ [mol%]	Temp [°C] / Time [min]	Conversion [%, GC-FID]	Selectivity P/D/H [%, GC-FID]
1	Batch/MW	0.01	180 / 30	90	99 / <1 / 0
2	Batch/MW	0.01	200 / 16	>99	99 / <1 / 0
3	Flow (1 mL min^{-1})	0.01	200 / 16	>99	99 / <1 / 0

Glasnov, T. N; Findenig, S.; Kappe, C. O. *Chem. Eur. J.* **2009**, *15*, 1001

Continuous Flow Cu-Catalyzed Azide-Alkyne Cycloaddition (CuAAC, "Click Chemistry")



Flow (acetone)
170 °C, 1.5 mL/min, 20 bar
(12 s residence time)

X-Cube
(200 °C, 150 bar)

cf. Cu/C: Lipshutz, B. H. et al. *Angew. Chem. Int. Ed.* **2006**, *45*, 8235

cf. flow click chemistry: Smith, C. D. et al. *Org. Biomol. Chem.* **2007**, *5*, 1559
Bogdan, A. R.; Sach, N. W. *Adv. Synth. Catal.* **2009**, *351*, 849

Fuchs, M.; Goessler, W.; Pilger, C.; Kappe, C. O., *Adv. Synth. Catal.* **2010**, *in press*

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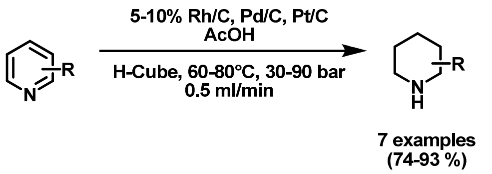
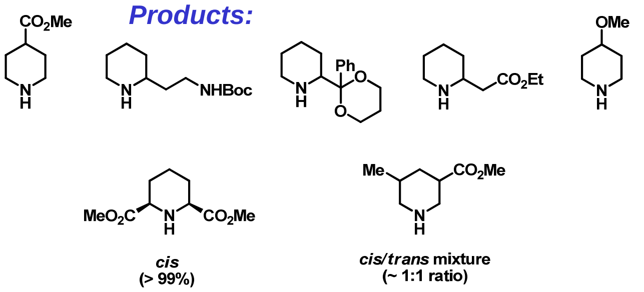
Continuous Flow Hydrogenations of Substituted Pyridines (H-Cube)



MW batch conditions (PtO_2):
AcOH, 8 bar H_2, 80 °C, 20-60 min

Piras, L. et al. *Synlett* **2008**, 1125

Products:



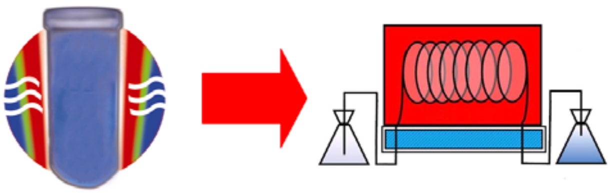
H-Cube
(100 °C, 100 bar)

Irfan, M.; Petricci, E.; Glasnov, T. N.; Taddei, M.; Kappe, C. O. *Eur. J. Org. Chem.* **2009**, 1326

Summary: Novel Process Windows - Transforming Microwave to Flow Chemistry

Microwave Chemistry *(Reaction Time)*

Flow Chemistry *(Residence Time)*



≤ 300 °C, ≤ 20 bar

≤ 350 °C, ≤ 200 bar

Translating microwave to flow chemistry: In a high-temperature/pressure microtubular flow device, many of the benefits inherent to microwave chemistry such as rapid heating/cooling and sealed vessel processing can be mimicked, including the generation of solvents in their supercritical state. In addition the scalability problem of microwave synthesis can be eliminated

Razzaq, T.; Glasnov, T, N.; Kappe, C. O. *Eur. J. Org. Chem.* **2009**, 1321

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University of Graz, Austria – www.maos.net

Christian Doppler Laboratory for Microwave Chemistry

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Dr. Toma N. Glasnov
Tahseen Razzaq
Markus Damm
Irfan Muhammed

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